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REMARKS

For reference, the text of page 2 and following of the Office Action is set forth below, with responses interlineated.

[Page 2]
DETAILED ACTION
Preliminary Note *As per telephonic confirmation with Richard Willson Jr on 9/10/2007, claims 1-24 are pending.*
Election/Restrictions
Applicant's election of the species (1) single stranded regions, (2) chromatography, and (3) denaturation in the reply filed on 8/11/2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).
Applicant's cancellation of claim 25 in the response filed 8/11/2007 is noted.
Claim Objections
Claim 9 is objected to because of the following informalities: there is an unpaired ")" after the word "contaminant". Appropriate correction is required.

The unpaired ";" has been cancelled from Claim 9.

Claim Rejections - 35 USC § 112
The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.
Claims 3-6,8-10,12 and 19-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
Claims 3, 4 and 19-22 recite the limitation "the product" in the first line of the claim. There is insufficient antecedent basis for this limitation in the claims or in claim 1, [Page 3] from which these claims depend. It cannot be determined what "the product" refers to: the affinity handle? the nucleic acid being separated? or does it refer to some product from which the nucleic acid is to be separated? The examiner will assume either of the latter two options. If these interpretations are the intent, Applicant is advised to amend claim 1 to recite a product, "wherein the product is either a nucleic acid to be purified, or a product (which can be either a nucleic acid or a non-nucleic acid product) from which undesired nucleic acid is to be separated".

In Claims 3-4 and 19-22, the word "product" has been replaced by -------captured nucleic acid—to follow the wording of Claim 1.

Claims 3 and 4 are also rejected under this section because it cannot be understood what the word "selective" in the phrase "a moiety that is sensitive to host genomic DNA contamination selective such as ... " means. For purposes of further examination, the examiner will construe this term to mean "during selective separation", based on the language of claim 1.

As claims 5 and 6 depend from claim 4, they are rejected under this section for the reasons discussed above.

In Claim 3, "selective" now reads –during selective separation—as helpfully suggested by the Examiner. The word has been cancelled from Claim 4. The confusion in wording is regretted.

Also regarding claims 3, 8, 9 and 10, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d). Since claim 12 depends from claim 9, it is rejected for the same reason. For purposes of further examination, the examiner will construe the limitations following the phrase "such as" to be optional.

Claims 3, 8, 9 and 10 have been re-worded to eliminate "such as".

Also regarding claims 8 and 9, the phrases "after another thermally based process" and "after another alkali based process" in claims 8 and 9, respectively, suffer from a lack of antecedent basis, because there is no initial thermally based process or [Page 4] alkali based process recited in these claims or in claim 1, from which these claims depend. Applicant may wish to either amend claim 1 to recite such initial processes, or simply amend claims 8 and 9 to recite, respectively, "after a thermally based process ... " and "after an alkali based process ... ". For purposes of further examination, the claims will be construed based on the latter suggestion.

In Claims 8 and 9, "another" has been replaced with –a— or –an-- as helpfully suggested by the Examiner.

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351 (a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21 (2) of such treaty in the English language.

Claims 1-4, 6-8,10,14 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Verdine et al (WO 98/00435).

With regard to claims 1,2 and 7, Verdine teaches a method comprising introduction of a single-stranded region of nucleic acid as an affinity handle into the desired nucleic acid, followed by capture of the desired nucleic acid by a technique that is selective for the characteristics of the affinity handle (see page 10, lines 1-5; page 11, line 1 through page 12, line 4). Verdine introduced a single-stranded region of nucleic acid into a desired nucleic acid by way of using the single-stranded region of nucleic acid as a primer to PCR amplify a target

nucleic acid. One of the primers was tagged with six successive 6-histaminylpurine residues (see page 9, lines 20-22 and page 10, line 3, "H_6-tagged primer"). Verdine denatured the resulting PCR product in 6M [Page 5] guanidinium-HCl (page 11, lines 6-7), thus exposing the single-stranded affinity handle. The tagged strand of the PCR product was immobilized on Ni^{2}+-NTA resin (page 11, lines 6-7), allowing it to be separated from the other strand. Note that either the tagged on non-tagged strand of the PCR product may be considered the "desired" product.
With regard to claims 3 and 4, note that the desired (or undesired) product (i.e. the tagged or non-tagged strand of the PCR product) comprises single-strandedness (i.e. it is a single stranded molecule).

Page 6 line 25 to page 7 line 7 of the Specification supports the recitation in Claim 1 of exposing purine base sites, selective thermal denaturation and renaturation, alkaline denaturation, the use of restriction enzymes yielding single-stranded overhangs, the use of oligonucleotide dTs, single-stranded DNA binding proteins, minerals, and the use of primers or other nucleic acid fragments such as complementary DNA are useful for introducing, enhancing, or stabilizing affinity handles (e.g., single strandedness) in the undesired (or desired) nucleic acids to facilitate capture and separation of the undesired (or desired) nucleic acid from the desired (or undesired) nucleic acids, carbohydrate or protein. Verdine is modifying his molecule by inserting the common his-tags, a very different and less desirable approach to the separation.

With regard to claim 6, Verdine teaches IMAC (see page 11, lines 1-7). strandedness (i.e. it is a single stranded molecule).

Verdine inserts single strandedness as a single strand of amino acids (a peptide) whereas Claim 1 recites Applicant's preexisting purine base sites.

With regard to claim 8, Verdine produced a product by PCR (page 10, lines 1-5). PCR comprises thermal denaturation.

Claim 1 recites purine base sites whereas Verdine uses the common His-tag. Applicants handles are composed of previously existing purine sites. Verdine's thermal cycles in his PCR process are for the sole purpose of allowing the Polymerase enzyme to copy individual strands of DNA. The denaturation occurring in this Verdine process is not directly utilized to create secondary or tertiary changes in the

products structure. Verdine uses his thermal cycle to modify the primary structure of the DNA, not to uncover existing purine sites.

With regard to claim 10, Verdine teaches PCR (page 10, lines 1-5), which comprises selective thermal denaturation and renaturation. This also meets the claim based on the species of "the use of primers".

The primers mentioned in Applicants' claim are to "facilitate *capture* and separation of the undesired (or desired)" product, not to create the product itself as primers are used in the PCR process.Applicants' primers are never part of their product, whereas Verdines are. Applicants' do not require the expensive polymerase and nucleotides both required by Verdine.

PCR denatures everything, and is not selective. Verdine must use higher temperatures, not required by Applicants. Verdine uses more than 10 cycles of heating and cooling whereas Applicants need only one cycle. Higher temperatures and repeated cycles risk degradation of product.

With regard to claim 14, Verdine teaches adsorption on chelated metal (page 11, lines 6-7).

Applicants teach selective adsorption after an induced structural change to expose preexisting affinity handles to the chelated metal. Verdine *adds* common his-tags (amino acids) which remain as part of his product.

With regard to claim 16, Verdine teaches a column (page 9, lines 5-6). It is noted that the claim term "spin" does not distinguish over Verdine, since any column could be spun. The claim as written only requires the "use" of spin columns; it does not require the columns to be spun.

Spin column is cancelled from Claim 16 without prejudice and replaced with preferred IMAC.

Claims 1, 2, 5, 7, 8 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Heisler et al (US 5,843,654). [Page 6]
Heisler teaches a method for the construction of recombinant Taq polymerases (see Example 2, beginning in column 59, especially lines 40-45). Heisler teaches cloning the recombinant genes into a plasmid that introduces a "His-Tag" (see column 62, lines 64-66 and column 63, lines 12-20). Heisler teaches purification of

the recombinant proteins on Ni++ column (column 63, lines 50-53). Heisler teaches that the production of the celllysates comprising the recombinant Taq polymerases includes heat lysis (column 64, lines 48-52), followed by a second heating step (column 64, lines 63-64).
With regard to claims 1, 2 and 7, Heisler teaches the introduction of a structural affinity handle ("His-Tag"), which may be regarded as single-strandedness, since the handle comprises a single strand of six histidine residues) to the desired moiety (the recombinant Taq), followed by capture of the desired or undesired nucleic acids by techniques which are selective for the characteristics of the affinity handle (purification on the Ni++ column). Although this may seem confusing, a careful analysis of the claim shows that all that is required is that desired or undesired nucleic acids are captured by techniques that are selective for the characteristics of the affinity handle. The claim does not require that an affinity handle be introduced into nucleic acids (although this is one option recited by the claim). The claim requires introduction (or enhancement or stabilization) of an affinity handle into desired or undesired nucleic acids or-moieties. The claim does, however, require that desired or undesired nucleic acids be captured. This limitation is inherently met by the method taught by Heisler. Heisler teaches thermal lysis of host cells (column 64, lines 48-52), which would release the nucleic acid [Page 7] content of the cells. Heisler teaches a secondary heating step at 75°C for 1 hour, whereas Applicant's example 5 in the specification (which also involves purification of recombinant Taq) heats for 80°C, but for 1 minute. If heating at 80°C for 1 minute is sufficient to alter the contaminating genomic DNA to allow it to interact with the chelated metal of the affinity column, then certainly a mere reduction of 5°C would be more than compensated for by the 60-fold increase in incubation time. In addition, the lysate would comprise some nucleic acids that were single-stranded even without the heating step (such as mRNA, tRNA and rRNA). Since Applicant's assert in their disclosure that it is the "exposure" of bases that results in the adsorption to chelated metals during IMAC (immobilized-metal affinity chromatography), then such would also have occurred when Heisler passed his cells lysates over the Ni++ columns.
With regard to claim 5, Heisler teaches the manufacture of recombinant Taq polymerase (see Example 2, beginning in column 59, especially lines 40-45).
With regard to claim 5, Heisler teaches the manufacture of recombinant Taq polymerase (see Example 2, beginning in column 59, especially lines 40-45).

Heisler makes no use of preexisting purine base sites as now recited in the clarified Claims. Heisler implies that both the Taq and the nucleic acids will bind to the Ni++ Columns. This is not a useful purification procedure unless Heisler demonstrated a selective elution of either the unwanted (nucleic acid) or wanted (His-Taq) molecule away from the Ni++-NTA, which he did not. The Applicant's method teaches that His-Tagging Taq polymerase (and thus altering the molecule's primary structure) is not necesarry.

With regard to claim 8, Heisler teaches that the production of the celllysates comprising the recombinant Taq polymerases includes heat lysis (column 64, lines 48-52), followed by a second heating step (column 64, lines 63-64).

The heat lysis in Heisler's method is for the sole purpose of lysing the cells. Heisler's method does not take advantage of any purine base site in the nucleic acid structure (e.g. single strandedness) for the separation. As mentioned above, these nucleic acids will probably bind along with the Taq Polymerase, which will make the separation less selective (nucleic acids being separated from the his-Taq).

With regard to claim 19, Taq is a protein.

Protein is now cancelled from Claim 19. Bacs, PACs and YACs are supported in Table A.

Claims 1-4, 7, 9-12, 16, and 20-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Pham et al (BioTechniques, 20(3):492-497 (1996)).
With regard to claims 1, 2, 7 and 9, Pham introduces single-stranded "affinity handles" into undesired nucleic acids by alkaline lysis (see figure 1), rapidly neutralized [Page 8] (page 493, column 1, first paragraph), followed by capture of the undesired nucleic acids (denatured single-stranded DNA and RNA) on SSAM matrix, which is selective for the characteristics of the single-stranded "affinity handles" (see page 492, column 2, first full paragraph and see page 493, column 1, first paragraph).
With regard to claims 3 and 4, Pham's product (plasmid) is double-stranded, whereas the undesired nucleic acids are single-stranded. Pham's product would be "sensitive" to contaminating genomic DNA.

Claim 1 has been clarified by reciting the preexisting nature of the purine base sites Applicants use as handles. It is difficult to see what Pham is doing because he uses SSAM matrix (not IMAC) and SSAM is not enabled as to composition and is no longer available. In any case, Pham is not exposing any preexisting purine base sites for any separation.

With regard to claim 10, alkaline lysis (see figure 1) would produce alkaline denaturation.

But not for the purpose of creating affinity handles. Ideally, alkaline lysis should precipitate all genomic DNA away from solution. This is not the case

since alkaline lysis is not 100% efficient. As a matter of fact, a majority of the fragments formed during a "standard" alkaline lysis procedure comes from mechanical shear.

> *With regard to claims 11 and 12, Pham refers to his product as "purified supercoiled DNA" (page 494, column 2). Furthermore, Pham electrophoresed samples of his product (see figure 2), which would inherently "remove" linear and open circular forms from the supercoiled form.*

Pham makes no use of affinity handles in this electro separation:

> *With regard to claim 16, Pham's method involves the use of spin columns (see title and page 493, column 1, first paragraph "CHROMA SPIN+ TE-400 Column").*

Spin columns are cancelled from Claim 1.

> *With regard to claims 20, 21 and 22, while Pham was attempting to purify plasmid (and thus, in Pham's view, the "product" would be a plasmid, meeting the limitations of claim 20), it is noted that the method also achieves a purification of RNA and genomic DNA, which bind to the SSAM matrix. Therefore, said RNA and genomic DNA may also be regarded as "products". The claim term "desired" does not distinguish over the method of Pham, because what is "desired" is nothing more than a mental state of the one who practices the method.*

Pham was not creating the affinity handles on purpose, and we don't know the nature of the SSAM interaction with the gDNA and RNA.

> *[Page 9]*
> *Claims 1-4, 6, 7,10,14-17,23 and 24 are rejected under 35 U.S.C. 102(e) as being anticipated by Willson et al (US 2004/0152076) or alternatively under 35 U.S.C. 102(a) as being anticipated by Murphy et al (WO 02/46398). As the disclosures of these references are identical, reference will only be made to teachings in US 2004/0152076.*
> *With regard to claims 1,2 and 7, Willson teaches an embodiment in which a deoxyribose tail is used as a tag to bind a PNA (peptide nucleic acid) to an IMAC column (paragraph [120]). This represents the introduction of a single-stranded region of nucleic acid as an affinity handle.*

A deoxyribose tail would be a modification of primary structure, not secondary or tertiary structure. Such a tail would not be produced by "comprising purine base sites previously present, by a process selected from the group consisting of: selective thermal denaturation and renaturation, alkaline denaturation or the use of restriction

enzymes yielding single-stranded overhangs, selectively to either the desired or the undesired moieties or nucleic acid" as recited in the present Claims.

With regard to claims 3 and 4, note that the desired product (i.e. the peptide nucleic acid) comprises single-strandedness (i.e. it is a single stranded molecule).
The single-strandedness here is not purposely created from some other state (i.e. secondary or tertiary structure modifications). Such a product would not be produced from "purine base sites previously present, by a process selected from the group consisting of: selective thermal denaturation and renaturation, alkaline denaturation or the use of restriction enzymes yielding single-stranded overhangs, selectively to either the desired or the undesired moieties or nucleic acid;".

With regard to claim 6, Willson teaches IMAC (paragraph [0120]).
Willson is not exposing preexisting purine base sites as set forth in the Claims. Willson requires that the purine bases be already exposed and makes no claims to exposing them prior to contact with the IMAC ligand.

With regard to claim 10, Willson teaches the "use of primers or other nucleic acid fragments" (the deoxyribose tail is an "other nucleic acid fragment"; paragraph [0120]).
The desired or undesired molecule(s) here is not purposely created from some other state (i.e. secondary or tertiary structure modifications). Such a product would not be produced from "purine base sites previously present, by a process selected from the group consisting of: selective thermal denaturation and renaturation, alkaline denaturation or the use of restriction enzymes yielding single-stranded overhangs, selectively to either the desired or the undesired moieties or nucleic acid;".

With regard to claim 14, Willson teaches IMAC (paragraph [0120]), which comprises adsorption on chelated metal (paragraph [0007]).
Willson uses IMAC but does not selectively expose preexisting purine base sites.

With regard to claims 15, 16, 17, Willson teaches multi-channel plates ("well plate"), spin columns and magnetic particles (page 5, Table A, Parameter: Support Shape). [Page 10]

Willson uses these items but does not selectively expose preexisting purine base sites.

With regard to claim 23, Willson teaches RPC (reverse phase chromatography; "Reverse Phase Resin", which implicitly teaches reverse phase chromatography; page 6, Table A, line 2 under heading "Preferred").

Applicants' purine base site is preexisting, not purposely created from some other state (i.e. secondary or tertiary structure modifications) Willson uses RPC but does not selectively expose preexisting purine base sites.

With regard to claim 24, Willson teaches HIC (hydrophobic interaction chromatography; page 5, Table A, last 3 lines under heading "Preferred").

Willson is not using HIC as a capture method for preexisting purine base sites as set forth in the Claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1.Determining the scope and contents of the prior art.

2.Ascertaining the differences between the prior art and the claims at issue.

3.Resolving the level of ordinary skill in the pertinent art.

4.Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to [Page 11] consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The inventorship has been reconsidered and is found still to be correct as stated in the formal papers of the Application.

Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over either Willson et al (US 2004/0152076) or Murphy et al (WO 02/46398) in view of Hawkins (US 5,898,071).
The teachings of Wilson and Murphy have been discussed. Neither of these references teaches processing multiple samples in parallel.
Hawkins teaches methods of nucleic acid purification and teaches that an "advantage of using a microtitre plate is that many samples can be isolated in parallel" (column 10, lines 54-60).
It would have been prima facie obvious to one of ordinary skill in the art at the time the invention of the instant application was made to modify the method of either Willson or Murphy to process multiple samples in parallel, because Hawkins teaches this to be advantageous.

The purposes of both Willson/Murphy and Hawkins are different and each does not selectively expose preexisting purine base sites, as recited in the Claims.

Conclusion
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Woolwine whose telephone number is (571) 272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.
[Page 12]
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).
Gary Benzion Ph.D SPE

The formal rejections having been addressed by the Amendments to the Claims and the clarified Claims having been distinguished from each of the references, prompt allowance is respectfully requested under the mandate of 35 USC 101.

Support for the Amendments occurs in the original Claims and Specification, no new matter or estoppel is involved in the Amendments, which are made to clarify the Claims.

The two month extension and any other necessary fee (small entity) can be charged to USPTO Deposit Account 200336 of Technology Licensing Co. LLC. Correspondence may be addressed to USPTO Customer No. 26830.

It is respectfully urged that no Terminal Disclaimer is required under the circumstances, but the Attorney will supply one if required. No new matter or estoppel is involved in these Amendments.

The Examiner is especially invited to indicate some allowable matter, and to telephone Applicants' Attorney if that would expedite prosecution and disposal of this Application.

Respectfully submitted,

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